REMARKS

These remarks are in response to the Office Action dated September 25, 1997. Claims 22-27 are pending in the present application. Claim 22 has been amended to incorporate the limitations of claim 26. Claims 25 and 26 have been canceled without prejudice.

Applicant notes the Examiner's concern regarding compliance with sequence rules 37 CFR 1.821 through 1.825. Applicant has filed for permission to use the sequence listing filed for the parent application 08/167,628 filed December 14, 1993, now U.S. Patent 5,408,040.

Further, the application is objected to because of alterations which have not been initialed and/or dated as required by 37 CFR 1.52(c). Applicant notes that passages on pages 2 and 5 were inadvertently underlined in the filed application. Replacement pages 2 and 5, which are identical to filed pages 2 and 5 excluding underlining, accompany the present Amendment. Applicant respectfully requests that these replacement pages be substituted for filed pages 2 and 5.

No new matter has been added. Claims 22-24 and 27 are pending and at issue. Applicant respectfully requests reconsideration of the present application.

THE INVENTION

The present invention provides methods for ameliorating a cell proliferative disorder by treating the disorder with an antibody which binds to connective tissue growth factor (CTGF).

I. REJECTIONS UNDER 35 U.S.C.§112, SECOND PARAGRAPH

Claims 22-27 stand rejected under 35 U.S.C.§112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant notes that this rejection is moot with respect to canceled claims 25 and 26. Applicant respectfully traverses this rejection as it may apply to the amended claims.

Specifically, the Examiner states that the claims are indefinite for encompassing non-elected inventions and that the claims should be amended to include methods in which antibodies are used as the CTGF reactive agent.

Applicant has amended claim 22 to incorporate the limitations of canceled claim 26. Claim 22 now recites a "...therapeutically effective amount of a composition containing an antibody that

binds to CTGF...". Applicant believes that amended claim 22 now clearly indicates the elected invention.

In addition, the Examiner states that claim 22 is indefinite for using the plural "diseases". Applicant has amended claim 22 to omit "diseases".

The Examiner states that claim 26 is indefinite for depending from a non-elected claim. As previously noted, Applicant has canceled claim 26 to further prosecution of the present application.

Consequently, in light of the amendment to claim 22 and in view of the previous discussion, Applicant respectfully requests that this rejection under 35 U.S.C.§112, second paragraph, be withdrawn.

II. REJECTIONS UNDER 35 U.S.C.§112, FIRST PARAGRAPH

Claims 22-25 and 27 stand rejected under 35 U.S.C.§112, first paragraph, because the specification, while being enabling for methods of inhibiting cell proliferation using anti-CTGF antibodies, does not reasonably provide enablement for the use of any possible CTGF reactive agent, nor for methods of treating undergrowth of cells using a CTGF reactive agent. Applicant notes that this rejection is moot with respect to canceled claim 25. Applicant respectfully traverses this rejection as it may apply to the amended claims.

As previously stated, Applicant has amended claim 22 to recite a "...therapeutically effective amount of a composition containing an antibody that binds to CTGF...". As noted by the Examiner on page 3, line 22, of the present Office Action, the present specification is enabling for methods of inhibiting cell proliferation using anti-CTGF antibodies. Applicant believes that amended claim 22 clearly reflects the scope of the present specification.

On page 4, lines 8-12, of the present Office Action, the Examiner states that the present specification does not enable the use of antagonists to CTGF for the purpose of cell growth stimulation. The Examiner alleges that it is not clear how the same group of antagonists can be used for both inhibition and stimulation of cell proliferation.

CTGF is a growth factor which may play a significant role in the normal development, growth and repair of various tissues. Typically, such growth factors interact with specific cell surface receptors to promote cell growth. Receptor proteins for most hormones, neurotransmitters,

growth factors, antigens, and other chemical and physical signals (*e.g.* light) are transmembrane proteins located in the plasma membrane of cells. The signal generated by stimulation of the receptor by the binding of its specific ligand is transduced across the membrane by a conformational change in the receptor which activates the cellular response machinery in the cytoplasm. Long-term exposure (*in vivo* or *in vitro*) to an agonist, such as a growth factor, can induce down-regulation of a given receptor. This is often due to a decrease in transcription of the gene(s) encoding the receptor protein, but it may also be due to a destabilization of the mRNA involved or of the assembled protein product, or to an increase in the removal of the receptor (e.g. by promotion of its internalization by endocytosis). For example, in the case of the nicotinic receptor of skeletal muscle, it has been shown that there is an activity-dependent inhibition of transcription of the receptor genes and a concurrent post-translational down regulation of receptor expression (Laufer *et al.*, *Mol. Neurobiol.* 3:1-54, 1989). In addition, receptors can become desensitized to an agonist when such a molecule is over produced. Therefore, long-term exposure to a growth factor can induce receptor down regulation and/or desensitization and result in failed or inefficient signal transduction.

Applicant believes that the method of the invention can be used to ameliorate a cell proliferative disorder due to an undergrowth of cells when the long-term exposure of the cells to CTGF contributes to such a disorder. As discussed above, long-term exposure of cells to CTGF may initiate the down regulation and/or desensitization of CTGF-specific cell surface receptor(s) resulting in the undergrowth of cells so affected. An antibody of the present invention can be used to prevent such long-term exposure by binding to CTGF and inhibiting CTGF-receptor interactions, thereby preventing receptor down regulation and/or desensitization when it is desirable to do so.

Accordingly, Applicant respectfully requests that this rejection under 35 U.S.C.§112, first paragraph, be withdrawn.

II. REJECTIONS UNDER 35 U.S.C.§103(a)

Claims 22-26 stand rejected under 35 U.S.C.§103(a) as being unpatentable over Pang and Hart in view of Smith *et al.* Applicant notes that this rejection is moot with respect to canceled claims 25 and 26. Applicant respectfully traverses this rejection as it may apply to the amended claims.

The Examiner states that it would have been obvious to substitute an anti-PDGF monoclonal antibody as taught by Hart in the method of Pang. Further, a person of ordinary skill in the art would have been motivated to do so in view of the disclosure of Smith *et al.* which suggests that such antibodies are known in the art to be useful as antagonists. On page 5, lines 22-23, of the present Office Action, the Examiner suggests that amendment of the claims to indicate that the antibodies of the invention do not cross react with PDGF would obviate the present rejection.

Applicant has amended claim 22 to recite a composition containing an antibody which binds to CTGF or fragments thereof, and that does not bind to PDGF or fragments thereof, to further prosecution of the present application.

Accordingly, Applicant respectfully requests that this rejection under 35 U.S.C.§103(a), be withdrawn.

In summary, for the reasons set forth herein, Applicant maintains that claims 22-24 and 27 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (619) 678-5070.

Please charge any additional fees, or make any credits, to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 12/24/97

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